Contrast between innovator drug- and generic drug-induced renal dysfunction on coronary angiography (CONTRAST study)

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Abstract

Background: Contrast-induced nephropathy (CIN) has gained increasing attention in clinical practice, particularly during coronary angiography (CAG). However, some ñbioequivalentò generic (GE) drugs are less effective than the innovator (IN) drug. Therefore, the aim of this study was to compare contrast media (IN drug)-induced renal dysfunction to contrast media (GE drug)-induced dysfunction.

Methods and Results: We enrolled 44 patients who underwent elective CAG or percutaneous coronary intervention (PCI) and randomly divided them into two groups that received contrast media (Iohexol, non-ionic and low-osmolality contrast agent) containing either IN drug (Omnipaque®) or GE drug (Iopaque®). Blood and urine sampling were performed before and after (24h and 48 h) CAG or PCI. Biochemical parameters in blood [serum creatinine, cystatin C, high sensitive-C reactive protein and pentraxin-3] and urine [urinary albumin/Cr and liver-type fatty acid binding protein/Cr] were measured. There were no significant differences in the biochemical parameters at baseline between the groups. In addition, there were no differences in changes in biochemical parameters in blood and urine before and after CAG or PCI between the groups, although 1 patient in the GE group had

Conclusion: The degree of contrast in Iopaque®-induced renal dysfunction was comparable to that in Omnipaque®-induced dysfunction.

Key words: contrast-induced nephropathy; coronary angiography; generic drug; innovator drug.

Contrast-induced nephropathy (CIN) has gained increasing attention in clinical practice (1-3). CIN refers to the acute deterioration of renal function seen after the administration of contrast media in the absence of other causes. Coronary stent implantation reduces restenosis after percutaneous coronary intervention (PCI) in patients with coronary artery disease (CAD) (4-6). Coronary angiography (CAG) also uses contrast media and is an important technique for the diagnosis and treatment of coronary restenosis.

Contrast media have direct toxic effects on renal tubular cells, and cause vacuolization, altered mitochondrial function and apoptosis (7). High-risk patients, such as older patients and those with diabetes mellitus (DM) and congestive heart failure, have a higher incidence of CIN (calculated to be 15-25 %) than that in the general population (about 2-3%) (8-11). Patients with CAD are at high risk and may have a higher rate of CIN. Renal failure after the administration of contrast media that requires in-hospital dialysis is associated with a poor outcome, including in-hospital mortality and poor two-year survival (9, 12). Thus, we need to prevent CIN in patients who undergo CAG or PCI.

The use of generic (GE) drugs has been increasing, primarily as a cost-saving measure in healthcare. GE drugs are typically 20 to 90% less expensive than the equivalent innovator (IN) drugs. The application of GE drugs is typically based on chemical-pharmaceutical data and the results of bioequivalence studies, which demonstrate that the GE product is similar to the reference medicine (13). On the other hand, previous studies have shown that some

ective than the IN drugs (13-15). In addition, it is not known whether the degree of contrast media (GE drug)-induced renal dysfunction is similar to that of contrast media (IN drug)-induced dysfunction.

Although CIN was defined in terms of serum creatinine (S-Cr), renal injury can also be assessed by high-sensitivity biomarkers, such as serum cystatin-C (Cys-C) (16-18) and urinary L-type fatty acid binding protein (L-FABP) (19-21). In addition, pentraxin-3 (PTX-3) is an inflammatory maker that is more sensitive than C-reactive protein (CRP) for the direct assessment of vascular injury (22).

Therefore, the aim of this study was to compare contrast media (IN drug)-induced renal dysfunction to contrast media (GE drug)-induced dysfunction using high-sensitivity biomarkers in patients with suspected CAD who underwent CAG or PCI.

Methods

Study population

We prospectively enrolled 44 patients who underwent elective percutaneous catheterization (CAG or PCI) because of suspected CAD at Fukuoka University Hospital. Patients who were Ó80 y old, and those who showed hemoglobin A1c >8.0 %, S-Cr >1.5 mg/dL or a past history of allergy to contrast media were excluded. The remaining patients were randomly divided into two groups [contrast media (Iohexol, non-ionic and low-osmolality contrast agent) containing either IN drug (Omnipaque®) (n=23, IN group) or GE

after adjusting for several factors [age, gender, body mass index (BMI) and S-Cr]. We excluded 4 patients after randomization because 3 in the IN group lacked biochemical data and 1 in the GE group did not undergo CAG. Finally, we analyzed 40 patients in the IN (n=20) and GE (n=20) groups. The presence of CAD was defined according to significant coronary stenosis (>50 %, at least one coronary vessel) by CAG. CIN was also defined as an increase in S-Cr of 25 % and/or 0.5 mg/dL within 48 h after exposure to the contrast media (3). The protocol of this study was approved by the ethics committee of Fukuoka University Hospital, and all subjects gave their written informed consent to participate. We collected all of the patient background data using the medical database of Fukuoka University Hospital.

Evaluation of coronary risk factors and patient characteristics

We compared the IN and GE groups with regard to coronary risk factors. We checked fasting serum samples. Coronary risk factors included age, gender, obesity [body mass index (BMI)], hypertension (HT), dyslipidemia (DL), DM and chronic kidney disease (CKD). Patients who had a current systolic blood pressure (SBP)/diastolic BP (DBP) Ó140/90mmHg or who were receiving antihypertensive therapy were considered to have HT. DM was defined using the Japan Diabetes Society Criteria or if the patient was being treated with an oral hypoglycemic agent or insulin. Patients with low-density lipoprotein cholesterol Ó140 mg/dl, triglyceride Ó150 mg/dl, and/or high-density lipoprotein cholesterol <40 mg/dl, or

therapy, were considered to have DL. Obesity was defined as a BMI >25 kg/m^2. The estimated glomerular filtration rate (eGFR) was determined using the abbreviated equation that the Japanese Society of Nephrology modified for Japanese based on the Modification of Diet in Renal Disease Study; 194 x [age (years)]$^{-0.287}$ x [serum Cr (mg/dl)]$^{-1.094}$ x [0.739 if female]. CKD was defined as an eGFR <60 mL/min/1.73m^2. Medications included angiotensin II type 1 receptor blocker (ARB)/angiotensin converting enzyme inhibitor (ACE-I), calcium channel blocker (CCB), ß-blocker, diuretics, nitroglycerin, nicorandil, statin and non-steroidal anti-inflammatory drugs (NSAIDs).

Measurement of blood and urinary biomarkers

Blood and urine samples were collected following an overnight fast by standard techniques before catheterization (at baseline), and at 24 h and 48 h after catheterization. Biochemical parameters in blood, including complete blood cell count, liver function [aspartate aminotransferase (AST), alanine aminotransferase (ALT)], renal function [blood urea nitrogen (BUN), Cr and Cys-C], electrolytes [sodium (Na), potassium (K) and chloride (Cl)], creatine kinase (CK), high-sensitivity CRP (hs-CRP) and PTX-3 were determined. Urinary (U)-Cr, the ratio of U-albumin (Alb) to U-Cr (U-Alb/U-Cr) and the ratio of U-L-FABP to U-Cr (U-L-FABP/U-Cr) were also analyzed. The concentrations of PTX-3 in plasma and L-FABP in urine were determined in duplicate by specific enzyme immunoassays

uctions (R&D Systems, Minneapolis, MN, and Perseus Proteomics Inc., Tokyo, Japan). At our laboratory, the intra- and inter-assay coefficients of variation for these parameters were each < 5 %.

Statistical analysis

Statistical analysis was performed using the Stat View statistical software package (Stat View 5; SAS Institute INC., Cary, NC). Data are expressed as the mean ± standard deviation (SD). The significance of differences was evaluated using the unpaired and paired t-test for continuous variables and the χ^2 test for non-continuous variables. A value of $p<0.05$ was considered significant.

Results

Baseline patient characteristics

Table 1 shows the baseline clinical characteristics in the IN and GE groups. In the IN group, the percentages (%) of HT, %DM and %DL were 85 %, 50 % and 95 %, respectively. There were no differences in these 3 factors between the two groups. In addition, there were no differences in %CKD, left ventricular ejection fraction (LVEF) or the volume of contrast media used between the two groups. The GE group had a significantly higher incidence of treatment with diuretic than the IN group and the IN group tended to have a higher incidence of treatment with nicorandil than the GE group, whereas there were no differences

Baseline biochemical parameters in blood and urine

As shown in Table 2, there were no significant differences in baseline biochemical parameters in blood and urine, including S-Cr, PTX-3, hs-CRP, Cys-C, U-Alb/U-Cr and U-L-FABP/U-Cr between the IN and GE groups.

Time-courses of various biochemical parameters in blood and urine during the study period

The time-courses of various biochemical parameters in blood and urine are shown in Figure 1. The IN group showed significant increases in S-Cr, Cys-C and U-L-FABP/U-Cr after 24 h compared with baseline. The levels of hs-CRP in the IN group after 48 h and in the GE group after 24 h and 48 h were significantly increased compared with those at baseline.

Differences in changes in various biochemical parameters in blood and urine before and after CAG or PCI

Next, we analyzed the differences in changes in parameters before and after 24 h CAG or PCI between the IN and GE groups (Figure 2). There were no significant differences in φS-Cr, φCys-C, φhs-CRP, φPTX-3, φU-Alb/U-Cr and φU-L-FABP/U-Cr between the groups

I minus the value at baseline). We also analyzed the differences in changes in the parameters before and after 48 h CAG or PCI between the IN and GE groups. There were no significant changes in the parameters after 48 h between the groups (data not shown).

Differences in changes in S-Cr before and after CAG or PCI with or without treatment with diuretic or nicorandil

Since the GE group showed a significantly higher incidence of treatment with diuretic than the IN group and the IN group tended to show a higher incidence of treatment with nicorandil than the GE group (Table 1), we analyzed the differences in cpS-C_{max} (cpS-C_{max} = the maximum value of S-Cr at 24-48 h after CAG or PCI minus the S-Cr at baseline) between patients with and without the use of diuretic or nicorandil (Figure 3). There were no significant differences in cpS-Cr_{max} between ~~the~~ patients with and without the use of diuretic or nicorandil.

Percentage of ~~the~~ patients with CIN or an increase in S-Cr after the use of contrast media

While none of the patients in the IN group had CIN after 48 h (Figure 4a), 1 patient in the GE group (5 %) had CIN (GE group vs. IN group, p=0.311). The patient with CIN had DM, HT, DL and renal dysfunction (S-Cr at baseline=1.4 mg/dl) and required a greater volume of

o the average volume of medium (126 ml). Since only 1 of the total patients had CIN, we divided the patients into ϕS-Cr_{max} > 0 (n=16) and 0ÓϕS-Cr_{max} (n=24) (Figure 4b). The percentages (%) of ~~the~~ patients with ϕS-Cr_{max} > 0 in the IN and GE groups were 45 and 35 %, respectively (GE group vs. IN group, p=0.519).

Discussion

First, we found that the degree of Iopaque® (GE drug)-induced ϕS-Cr was comparable to that of Omnipaque® (IN drug)-induced ϕS-Cr, and only 1 patient in the GE group had CIN. Second, there were no differences in the changes in high-sensitivity biomarkers (Cys-C, PTX-3 and U-L-FABP/U-Cr) between the GE and IN groups, although these levels increased after catheterization.

In this study, GE drug-induced ϕS-Cr was similar to IN drug-induced ϕS-Cr. Since GE drugs have the same basic composition and properties as IN drugs (13, 23), our data should be reasonable. On the other hand, GE drugs are approved without testing by clinical trials. The validity of the current criteria for the interchangeability of IN and GE drugs remains controversial and may compromise the response and/or safety of patients. Previous reports have indicated that some ñbioequivalentò GE drugs are less effective than their respective IN drugs (14, 15, 23). Since these drugs are therapeutic agents, rather than diagnostic reagents like contrast media, the effect of GE contrast media in the present study was comparable to that of IN contrast media. In addition, we excluded patients with S-Cr >1.5

er normal renal function or only mild renal dysfunction. We selected patients who underwent elective catheterization, but not emergency catheterization, although emergency PCI has been shown to be a risk factor for CIN (24, 25). Finally, we used Iohexol, which is a non-ionic and low-osmolality contrast media, in this study because the type of contrast media used in patients with renal impairment may minimize the onset of CIN (8). These factors may make it difficult to distinguish between the effects of IN and GE drugs. This fact may also be associated with the fact that only 1 patient in the present study had CIN (2.5 %), whereas high-risk patients in previous reports have shown a higher incidence of CIN (15-25 %) (8-11).

The level of S-Cr is a definitive parameter for the diagnosis of CIN (3). There are many useful parameters for the evaluation of renal function, such as Cys-C and U-L-FABP/U-Cr. Cys-C is more sensitive than S-Cr for rapidly detecting acute changes in renal function (16, 17). Liu *et al*. suggested that the increase in Cys-C reaches a maximum within 24 h after exposure to contrast media (18). Although we also observed significant differences in changes in Cys-C after 24 h in the IN group, there was no difference between the IN and GE groups. Moreover, the endothelial toxicity of contrast media induces endothelial dysfunction as well as inflammation, oxidative stress, thrombosis, and altered vasomotor balance (7, 26). U-L-FABP is upregulated by stresses such as ischemia, toxins and an increase in free fatty acids (19) and can be used to help predict and monitor the progression of renal disease (20). The levels of U-L-FABP/U-Cr were also significantly increased after 24 h in the IN group,

ences in the changes in U-L-FABP/U-Cr between the groups. Thus, there were no differences in renal function after exposure to contrast media, despite the use of two excellent clinical markers. We also analyzed inflammatory markers, such as hs-CRP and PTX-3. Although both hs-CRP and PTX-3 significantly increased after 24 h in all patients ($p<0.01$ and $p<0.05$, respectively), there were no differences between the IN and GE groups. Since PTX-3 is a short form of CRP and an acute-phase reactant that is produced at the site of inflammation by macrophages, dendritic cells, neutrophils, fibroblasts, endothelial cells and smooth muscle cells (22), contrast media may influence the activation of these cells.

In this study, the GE group had a significantly higher incidence of treatment with diuretic and the IN group tended to have a higher incidence of treatment with nicorandil, although we randomly divided the patients into the IN and GE groups using computer software. Diuretic therapy, in addition to aging, DM, baseline renal insufficiency, higher doses of contrast media and so on, is associated with a higher risk of CIN (27, 28). Nicorandil is an ATP-sensitive potassium (KATP) channel agonist and a nitric oxide donor. KATP channel reduces renal injury due to ischemia and reperfusion, which suggests that nicorandil may protect the kidney from ischemic injury associated with the use of contrast media (29, 30). Although diuretic and nicorandil therapy may affect renal function after the use of contrast media, there were no significant differences in $\varphi S\text{-}Cr_{max}$ between the patients with and without the use of diuretic or nicorandil.

rnatives to the more costly IN drugs used in clinical medicine today. The IN drug (Omnipaque®) and the GE drug (Iopaque®) used in the present study cost 9,358 and 7,430 yen/100mL, respectively. Since the average volumes of contrast media used in this study for the IN and GE drugs were 125.7 and 125.2 mL/person, respectively, the total costs of the IN and GE drugs were 11,763 and 9,302 yen/person, respectively. This difference (2,461 yen/person) represents a significant cost savings.

There are many strategies for the prevention of CIN after the use of contrast media e.g., hydration, and the administration of mannitol and furosemide (9, 31-33). Although therapeutic prevention strategies are being extensively investigated, there is still no definitive answer (9). In this study, the patients did not receive specific treatments for the prevention of CIN and received only a standard infusion of intravenous fluids. There was no difference in the volume of infusion between the IN and GE groups. In addition, the development of CIN seems to depend on the amount of contrast agent given. However, there was no difference in the volume of contrast media between the IN and GE groups, and the volume was lower than in previous reports (32-34).

This study has several study limitations. First, the sample size was relatively small. However, we randomly divided the patients into IN and GE groups after adjusting for several critical factors (age, gender, BMI and S-Cr). Second, the measurements were performed under various oral medications. Although many of the patients were taking diuretics and NSAIDs that might influence the onset of CIN, there was no significant

he IN and GE groups. In addition, there were no differences in φS-Cr, φCys-C, φhs-CRP, φPTX-3, φU-Alb/U-Cr or φU-L-FABP/U-Cr between patients with and without the use of diuretics or nicorandil.

In conclusion, the degree of contrast in Iopaque® (GE drug)-induced renal dysfunction was comparable to that in Omnipaque® (IN drug)-induced dysfunction.

Disclosure

K.S. and S.M. have received lecture honoraria and research grants from Daiichi-Sankyo Co. Ltd. K.S. is the Chief Director and S.M. is a Director of NPO Clinical and Applied Science, Fukuoka, Japan.

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Figure 1.

Time-courses of various biochemical parameters in blood and urine during the study period in the IN (black lines) and GE (gray lines) groups. *$p<0.05$ vs. before CAG or PCI (at baseline).

Figure 2.

Differences in changes in various biochemical parameters in blood and urine before and 24 h after CAG or PCI in the IN (black bars) and GE (gray bars) groups.φ indicates the value 24 h after CAG or PCI minus the value at baseline. N.S., not significant.

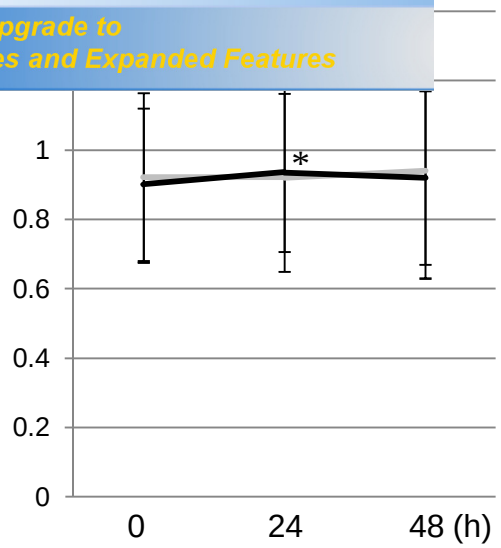
Figure 3.

Differences in changes in S-Cr between before and after CAG or PCI with (dotted bars) or without (open bars) treatment with diuretic (a) or nicorandil (b).φS-Cr_{max} indicates the maximum value of S-Cr at 24-48 h after CAG or PCI minus S-Cr at baseline. N.S., not significant.

Figure 4.

Percentages (%) of CIN (a) and ~~the~~ patients with φS-$Cr_{max} > 0$ (b) in the IN (black bars)

indicates the maximum value of S-Cr at 24-48 h after CAG or PCI minus S-Cr at baseline. N.S., not significant.



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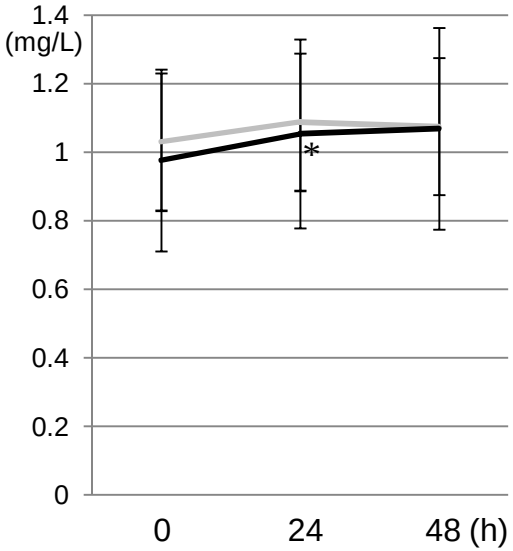

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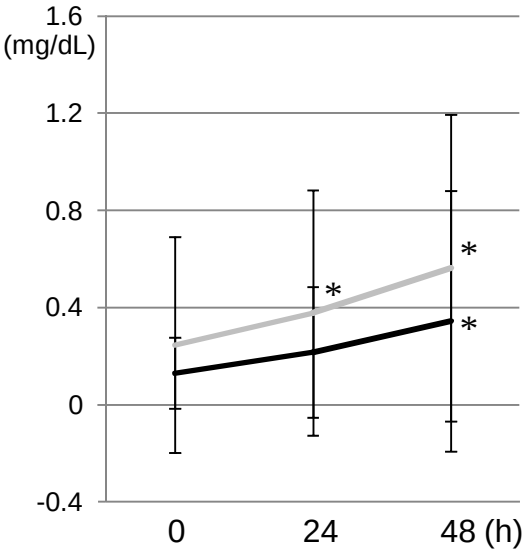

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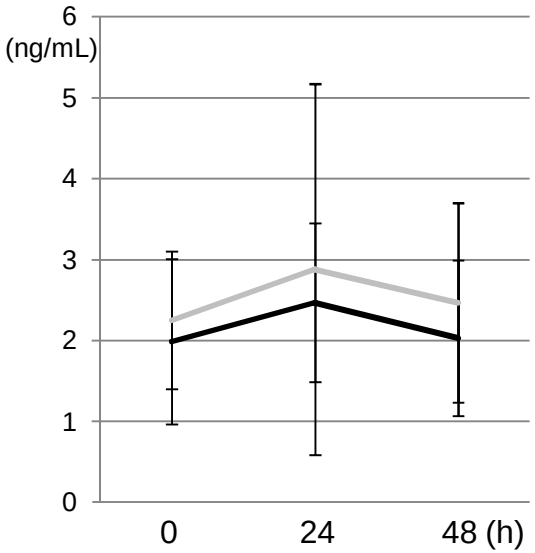

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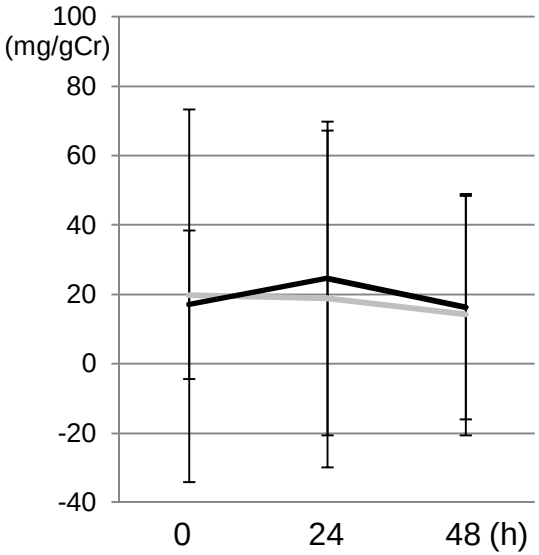

f. U-L-FABP/U-Cr

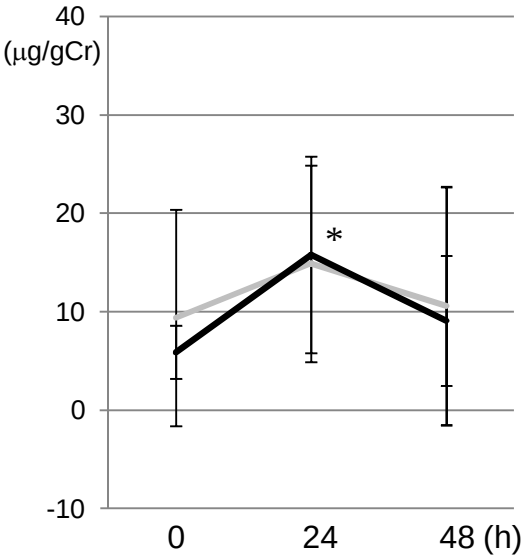

Figure 1.
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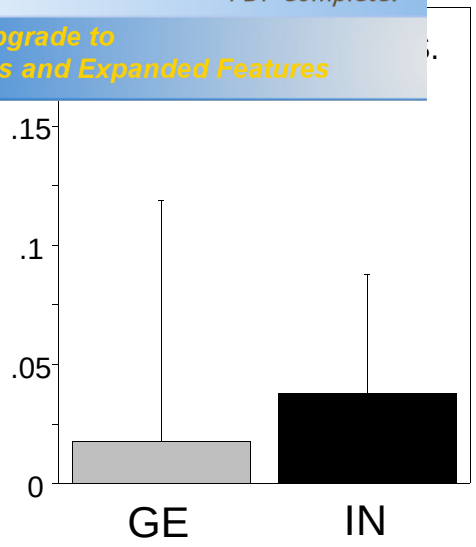
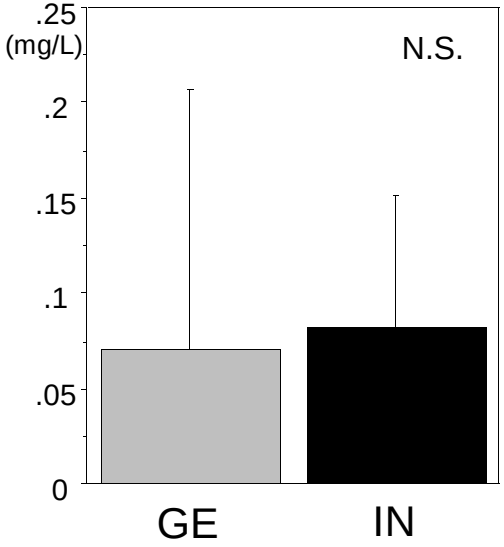
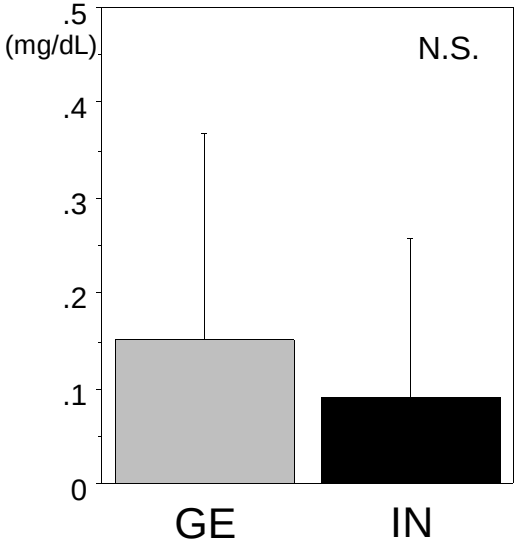


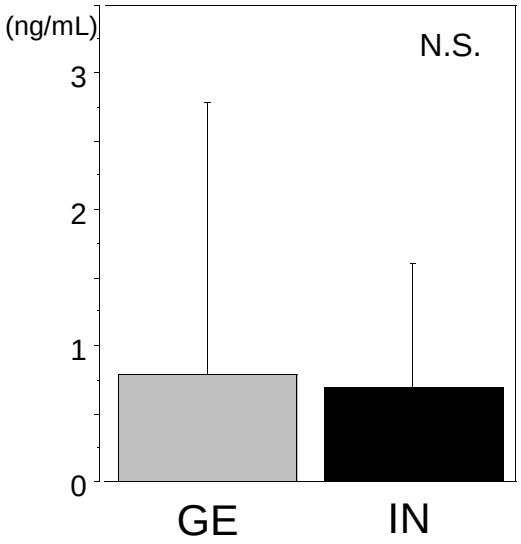
b. qpCys-C



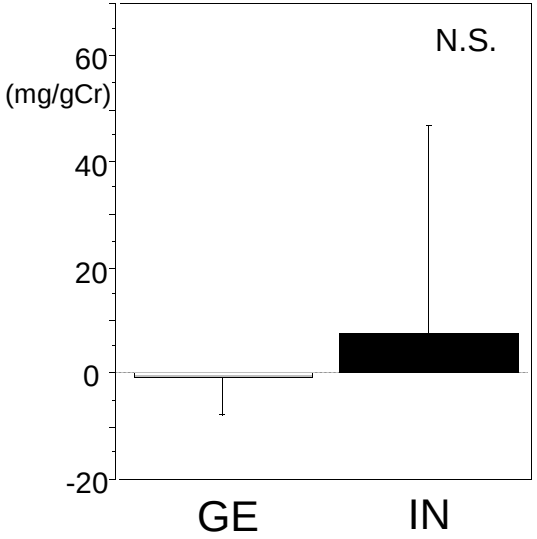
c. qhs-CRP



d. qPTX-3



e. qU-Alb/U-Cr



f. qU-L-FABP/U-Cr

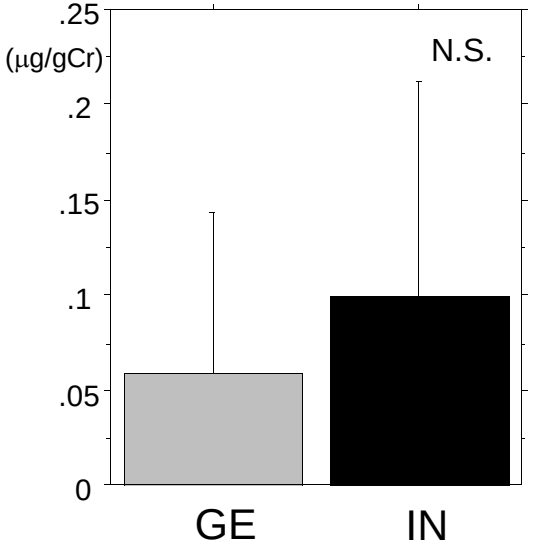


Figure 2.
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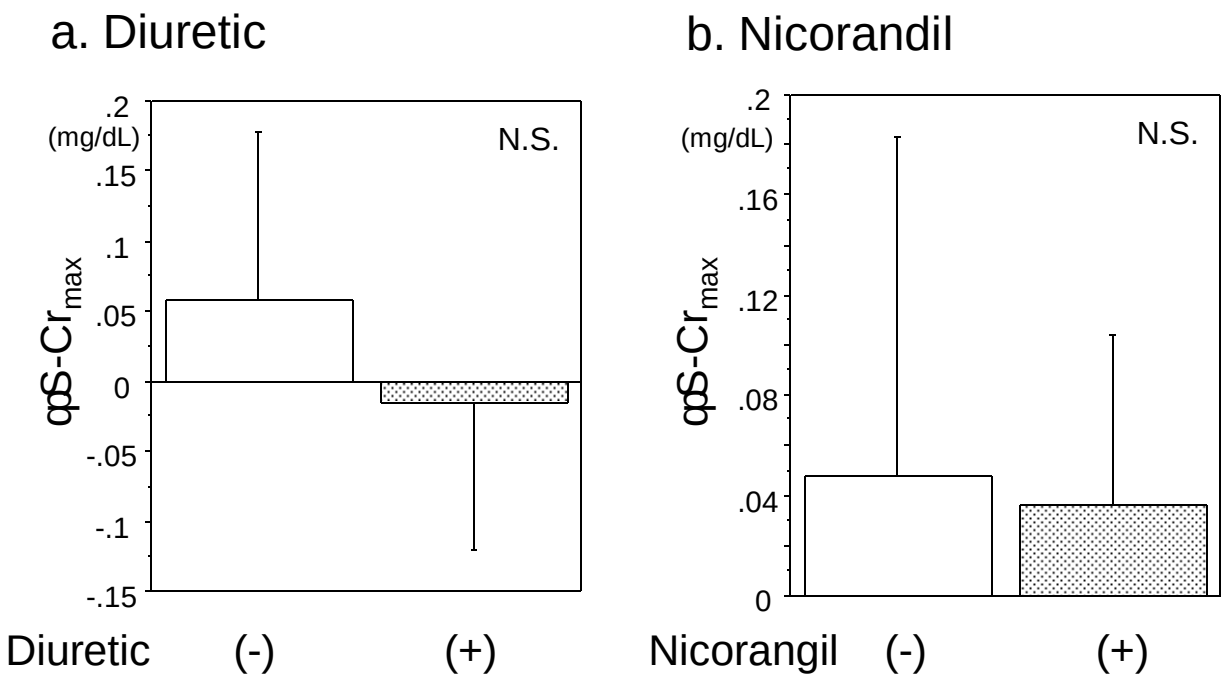

Figure 3.
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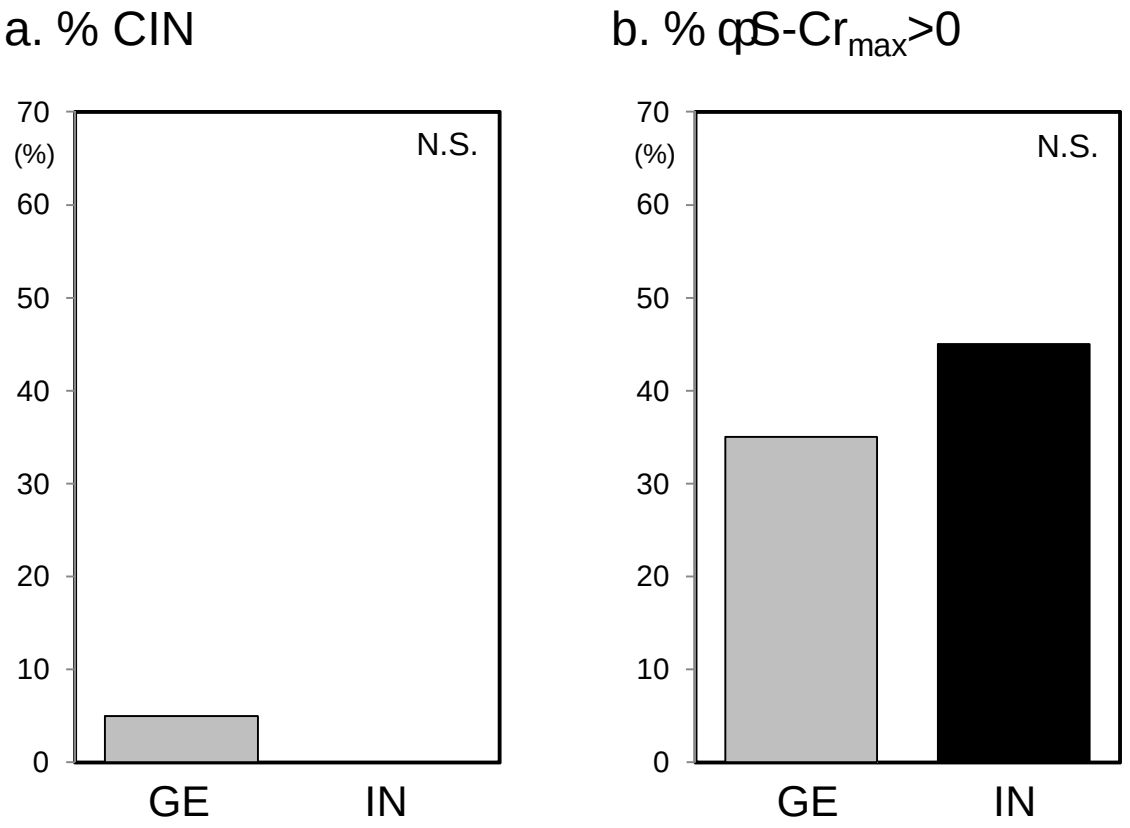

Figure 4.
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t characteristics.

	IN (N=20)	GE (N=20)	P value
	68±9	72±6	0.09
Male, %	75	65	0.50
BMI, kg/m²	23±3	23±3	0.85
HT, %	85	100	0.07
DM, %	50	30	0.21
DL, %	95	90	0.56
CKD, %	35	40	0.75
CAD, %	95	90	0.55
LVEF, %	61±14	64±11	0.58
Volume of contrast medium, mL	126±63	125±67	0.98
Infusion volume of intravenous fluids, ml	1375±425	1350±813	0.90
Medication			
ARB/ACE-I, %	75	65	0.50
CCB, %	60	65	0.75
β-blocker, %	15	15	0.99
Diuretic, %	5	30	0.04
Nitroglycerin, %	25	10	0.22
Statin, %	80	85	0.69
Nicorangil, %	40	15	0.08
NSAIDs, %	35	15	0.15

IN, innovator; GE, Generic; BMI, body mass index; HT, hypertension; DM, diabetes mellitus; DL, dyslipidemia; CKD, chronic kidney disease; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; ARB, angiotensin II type 1 receptor blocker; ACE-I, angiotesin converting enzyme inhibitor; CCB, calcium channel blocker; NSAIDs, non-steroidal anti-inflammatory drugs.

ical parameters in blood an urine.

	IN (N=20)	GE (N=20)	P value
	5470±1422	5905±1737	0.39
Hb, g/dL	13.0±1.7	13.0±1.5	0.93
BUN, mg/dL	16.1±4.6	17.6±4.7	0.33
Cr, mg/dL	0.9±0.2	0.9±0.2	0.79
eGFR, ml/min/1.73m²	64.9±14.4	61.4±14.0	0.44
Na, mEq/L	140±3	140±2	0.90
K, mEq/L	4.2±0.4	4.3±0.5	0.88
Cl, mEq/L	101±2	105±3	0.36
AST, IU/L	23±6	24±6	0.45
ALT, IU/L	23±11	25±13	0.63
CK, IU/L	116±106	84±37	0.22
hs-CRP, mg/dL	0.13±0.16	0.25±0.45	0.30
PTX-3, ng/mL	2.0±1.02	2.3±0.9	0.41
Cys-C, mg/L	1.0±0.3	1.0±0.3	0.58
U-Cr, mg/dL	81±38	83±64	0.88
U-Alb/U-Cr, mg/gCr	17±21	20±54	0.84
U-L-FABP/U-Cr, εg/gCr	0.06±0.03	0.09±0.11	0.21

IN, innovator; GE, Generic; WBC, white blood cell; Hb, hemoglobin; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate; Na, sodium; K, potassium; Cl, chloride; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CK, creatine kinase; hs-CRP, high-sensitive C-reactive protein; PTX-3, pentraxin-3; Cys-C, cystatin-C; U-Cr, urinary creatinine; U-Alb/U-Cr, U-albumin/U-Cr; U-L-FABP/U-Cr, U-L-type fatty acid binding protein/U-Cr.